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Introduction, Background, and Definitions

Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

Principle 7, the Nuremberg Code

The protection of individuals who volunteer to participate in research is essential to the ethical conduct of research. Such protections were not explicitly and systematically addressed in the United States, however, until the late 1940s, when scientists and policy makers recognized the need to respond to crimes committed by Nazi scientists during World War II. Since then national and international policies have evolved to create a system of protections requiring the involvement of investigators, research sponsors, research institutions, health care providers, federal agencies, and patient and consumer groups. This evolution is worth tracking to appreciate what brings this report to the forefront at this time; that is, how can this complex system of protections be assessed in a reliable and valid way to ensure that it is effective, efficient, and accountable—that "proper preparations" have been made and that "adequate facilities" have been provided to protect the experimental subjects of research?

ORGANIZATION OF THE REPORT

Before beginning the discussion leading to the recommendations contained within this report, the committee notes that this document focuses narrowly on

the accreditation of programs that are charged with the responsibility of protecting individuals who volunteer for research. This first chapter provides the relevant background preceding this work, as well as discussion pertaining to the committee's concept of a human research participant protection program (HRPPP) and related terminology. Chapter 2 explores various models of accreditation. It also focuses on how accreditation might apply to activities surrounding protection of human research participants and explores the process for such a system.

Chapter 3 centers on the issue of standards; that is, what values and measurements should be used to address an organization's level of performance and expectations for activities that affect the protection of participants in human research? In response to its charge, the committee reviewed the draft Public Responsibility in Medicine and Research (PRIM&R) standards and those developed by the National Committee for Quality Assurance (NCQA). Chapter 3 presents the committee's recommendations about standards for accreditation.

Chapter 4 focuses on issues in evaluating and analyzing a system of accreditation. In response to the committee's third task, this chapter includes committee recommendations for steps that the federal government should take to collect and analyze data that can be used to monitor and evaluate how well the system for protecting human research participants is operating.

A SHORT HISTORY OF HUMAN SUBJECTS PROTECTIONS IN THE UNITED STATES

In response to the atrocities committed by German scientists during World War II, the Nuremberg Military Tribunal originated the Nuremberg Code, a set of 10 principles for research involving human participants, including an absolute requirement for voluntary consent (Nuremburg Code, 1946–1949;*United States v. Karl Brandt et al*. The Medical Case 1946–1949). The Nuremberg principles placed primary responsibility on the investigator to ensure that research was ethically conducted. At the same time that the Nuremberg Trial was proceeding, anticipating the need for a rapid response to concerns about research abuses, the American Medical Association adopted its first code of research ethics for physicians in 1946, outlining principles to be followed in conducting research with human subjects (AMA Judicial Council, 1946).

Over the ensuing two decades, U.S. policy in this area evolved, addressing prohibitions on research involving vulnerable or special populations and eventually requiring independent review of research and written consent for "hazardous" research (ACHRE, 1995). The Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act required the Food and Drug Administration (FDA) to evaluate new drugs for safety as well as efficacy, significantly expanding the power of the federal government to influence the conduct of clinical

trials in particular.[1] One of the provisions of this act required the informed consent of participants in the testing of new drugs. The federal policies were slowly moving away from reliance on the investigator as the sole focus of decision making about ethical research and more toward a policy that required independent review of research and retrieval of voluntary informed consent. This meant that the responsibility, although still on the investigator, was also being placed on the institutions that support and conduct research.

By the 1960s, however, few research institutions had in place a system for protecting research subjects, despite requests by the National Institutes of Health (NIH) that they do so (Faden and Beauchamp, 1986). A 1966 U.S. Public Health Service (PHS) policy required independent review of research by a committee of the investigator's "institutional associates" (PHS, 1966). Later, NIH would create the Office for Protection from Research Risks (OPRR) and take the lead in the protection of research subjects in research conducted or sponsored by the U.S. Department of Health and Human Services (DHHS).

The need for enhanced efforts to protect research subjects was underlined in 1966 when Henry Beecher published an article presenting 22 examples of "unethical or questionably ethical studies" that had appeared in mainstream medical journals (Beecher, 1966). One of these studies involved injection of the hepatitis virus into children seeking admission to the Willowbrook State School for the Retarded in New York. Although parental consent was obtained, it was likely uninformed and certainly suspect because of undue influence, that is, concerns of parents that their children could not be enrolled in the school if they refused to participate (ACHRE, 1995). Then, in 1972, details emerged about the Tuskegee Syphilis Study, begun in the 1930s (Heller, 1972). The study attempted to trace over several decades the natural history of syphilis in poor, African-American males living in Alabama. Not only were the participants not told the purpose of the study, but they were also led to believe that they were receiving treatment (Gamble, 1997; Heller, 1972; Jones, 1981). PHS deemed the study unethical and stopped it, offering the surviving participants antibiotic treatment.

A PHS advisory panel reviewing the Tuskegee study determined that existing procedures for the protection of research subjects were inadequate and that the U.S. Congress should establish a "permanent body with the authority to regulate *at least* all federally-supported research involving human subjects" (Tuskegee Syphilis Study Ad Hoc Advisory Panel, 1973, p. 23). Subsequent congressional hearings led to passage of the National Research Act, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) to provide analyses of the ethics and policies related to the conduct of research with human subjects.[2]

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[1] Federal Food, Drug, and Cosmetic Act of 1938. P.L. No. 75-717, 52, Stat. 1040, as amended 21 U.S.C. 31 et seq.

[2] National Research Act of 1974. P.L. No. 93-348 (1974).

In 1979, the National Commission published *The Belmont Report*, which identifies three basic principles for the ethical conduct of research with human subjects: respect for persons, beneficence, and justice. In response to this report, DHHS and FDA revised their regulations, creating in 1981 the Federal Policy for the Protection of Human Subjects in Research.[3] The National Commission described the then-emergent structure and function of ethics review boards at research institutions, which later became known as institutional review boards (IRBs). IRBs became the roof beam in the framework for the protection of the rights and interests of human participants in research and remain so today.

In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (the President's Commission) was established. Two of its reports focused on the system of protection of human participants in research (President's Commission, 1981, 1983). In *Implementing Human Research Regulations*, the President's Commission recommended that "There should be a uniform Federal system documenting the implementation of the regulations through prior assurance and periodic site visits" (President's Commission, 1983, p. 3).

Eventually, the federal government would attempt to standardize the human subjects regulations across agencies and departments. In 1991, the regulations, now known as the "Common Rule" (Subpart A, 45 CFR 46), were simultaneously published in the *Federal Register* by 15 departments and agencies. By 2001, 18 agencies have adopted the Common Rule, and numerous additional international documents and guidelines have been developed and revised (see Box 1-1). The regulations used across the federal government prescribe requirements for research involving human subjects, including the functions, operations, and compositions of IRBs; IRB review of research; record keeping; and requirements for informed consent.

MORE RECENT EVENTS

Advisory Committee on Human Radiation Experiments

In 1993, the nation was shocked by a series of news articles in the *Albuquerque Tribune* that revealed experiments involving injection of plutonium into humans. This touched off national press coverage and subsequent revelations about Cold War-era radiation experiments conducted with civilian and military populations. In response, President Bill Clinton established the Advisory Committee on Human Radiation Experiments (ACHRE) to investigate reports of federally sponsored human research involving radioactive materials conducted

[3] 45 CFR 46; the FDA regulations are at 21 CFR 50,56

BOX 1-1 Relevant International Codes

Research is a global enterprise. U.S. commissions have built on and worked in parallel with codes developed elsewhere in the world, some of which also set a context the present committee's work. Several international codes articulate principles for the ethical conduct of research. The **Declaration of Helsinki** is perhaps the best known among these. In its current form, the declaration contains 32 statements of principle to guide medical research. Its conceptual foundation is the medical ethics of the doctor-patient relationship, and this is extended to medical research via an investigator-subject relationship. The declaration opens with general statements of moral norms, the duties of physicians, and the subordinate role of science when it comes into conflict with the human rights of human subjects, followed by sections on research per se and research combined with medical care.

The **Council for International Organizations of Medical Sciences** (CIOMS) prepares the *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. The first CIOMS guidelines were published in 1982, followed by revision in 1993, and they are being revised, with public release expected in the next year (CIOMS, 1982, 1993).

The **International Conference on Harmonisation** has developed detailed guidelines specific to drug trials and for good clinical practice (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996, 1997) and many other guidelines on other aspects of testing of pharmaceutical products. The International Conference on Harmonisation was formed in 1990 and involves government agencies and pharmaceutical trade organizations from the European Union, Japan, and the United States (International Conference on Harmonisation, 1998). Its guidelines are not just for research that crosses national borders but, in fact, constitute guidance for trials of any size and are recognized formally by the Food and Drug Administration.

Several governments, including those of India and Canada, have prepared guidelines for research that are recognized by the U.S. Office of Human Research Protections (CECHR, Indian Council of Medical Research, 2000; NSERC, 2000; OHRP, 2000a). The **Indian Council of Medical Research** guidelines apply to biomedical research, and the **Tri-Council Statement** from Canada applies to research under the Natural Sciences and Engineering Council, the Social Sciences and Humanities Research Council, and the Institutes of Health Research.

between 1944 and 1972. ACHRE's work is a direct precedent to several current activities. As part of its charge, ACHRE also assessed the current state of pro tections for research subjects. In its final report, ACHRE concluded that it had found "evidence of serious deficiencies in some parts of the current system" (ACHRE, 1995, p. 797). In particular, ACHRE cited variability in the quality of IRBs, confusion on the part of research participants about whether they were to receive therapeutic benefit from volunteering for studies, and concern about the adequacy of the consent process. ACHRE urged that (1) federal oversight of human subject protections focus on outcomes and performance rather than paperwork reviews and intermittent audits for cause, (2) sanctions for violation be authorized and be in proportion to the seriousness of the violation, and (3) protections be extended to research that is not federally funded.

A study commissioned by NIH and published after release of the ACHRE report corroborated many of the ACHRE committee's findings. The study was based on a survey of IRBs and investigators at research institutions holding a federal assurance agreement with NIH. It found that an estimated half million people were involved in research under IRB-reviewed protocols and that the number of protocols had more than quadrupled in the two decades since the National Commission had last surveyed IRBs (Bell et al., 1998). That report concluded that the system of protection was by and large functioning adequately, but it did point to a mounting workload and the intermittent emergence of research scandals.

ACHRE also called for the creation of a national commission "to provide for the continuing interpretation and application of ethics rules and principles for the conduct of human subject research in an open and public forum" (ACHRE, 1995, p. 821). President Clinton's executive order creating the National Bioethics Advisory Commission (NBAC) implemented this recommendation.[4]

The National Bioethics Advisory Commission

NBAC was established by executive order in October 1995 and was asked by President Clinton to look into the protection of human subjects in research, with "protection of the rights and welfare of human research subjects" listed as its first priority (Clinton, 1995). As one of its first actions, in May 1997 NBAC unanimously resolved that "no person in the United States should be enrolled in research without the twin protections of informed consent by an authorized person and independent review of the risks and benefits of the research" (NBAC, forthcoming-b, p. 26). NBAC issued subsequent reports on research involving

[4] NBAC's establishment was also a culmination of long-standing interest in a bioethics commission among members of Congress, such as Senators Mark Hatfield and Edward Kennedy and Rep. Henry Waxman, as well as a 1993 congressional report and the President's Science Advisor, John H. Gibbons (OTA, U.S. Congress, 1993).

those with impaired decision-making capacity (NBAC, 1998), research using human biological materials (NBAC, 1999a), and ethical issues in human stem cell research (NBAC, 1999b), all of which address issues of research oversight and IRB function. Forthcoming reports will address ethical principles for U.S. interests conducting clinical trials abroad (NBAC, forthcoming-a) and describe a 5-year review of the adequacy of the system of human subjects protection in the United States (NBAC, 2001b).

Reports from DHHS Office of the Inspector General

In June 1998, the Office of the Inspector General (OIG) of DHHS issued a report, *Institutional Review Boards: A Time for Reform* (DHHS OIG, 1998b). The report's foremost finding was that "the effectiveness of IRBs is in jeopardy" (p. ii) and found that IRBs are facing overwhelming demands. A system that was originally devised as a volunteer effort to oversee a much smaller research effort in the 1970s was characterized as contending with its growing burden with scant resources. Recommendations included better training of IRB members and investigators, recasting of federal requirements to give IRBs more flexibility yet require more accountability, reduction of potential conflicts of interest among IRBs to enhance independence, and improvement of feedback to IRBs about developments in multisite trials and prior reviews of research plans. Echoing one of the charges to the present committee, the DHHS OIG report called for greater attention to the development and reading of indicators of how well IRBs were doing their job.

A Time for Reform was the flagship in a convoy of DHHS OIG reports on protection of human research subjects. Three other DHHS OIG reports came out at the same time: (1) promising approaches to improving protections, (2) a description of the IRB process, and (3) a description of the emergence of independent boards, that is, IRBs that mainly review drug, device, and biologics trials sponsored by private industry under FDA regulations (DHHS OIG, 1998c,d,e). In April 2000, the DHHS OIG issued an update on *A Time for Reform*. It noted the increased enforcement efforts of both OPRR and FDA but little overall progress on its other recommendations (DHHS OIG, 2000b). DHHS OIG staff testified at hearings in both the U.S. House and U.S. Senate as Congress turned its attention to human subject protections in the year 2000 (Grob, 2000). The April 2000 DHHS OIG update specifically lauded the efforts of PRIM&R to develop standards for accreditation of IRBs and research institutions. A pair of reports published in June 2000 focused on recruiting human subjects, with one describing pressures in industry-sponsored clinical research and the other listing sample guidelines for practice (DHHS OIG, 2000c,d).

Shutdowns of Clinical Research at Academic and VA Medical Centers

In May 1999, OPRR halted human research studies at Duke University Medical Center, sending shock waves throughout the research community. Within a year, FDA and OPRR proceeded to halt all or some clinical research projects at seven other research centers.[5] These events focused the attention of research administrators on IRB operations and human subject protections with an intensity not seen in two decades. In November and December 2000, the newly established DHHS Office for Human Research Protections (OHRP)[6] issued "compliance determination" letters that found that studies in the intramural program at NIH were out of compliance with federal regulations.[7] OPRR/OHRP has restricted or suspended multiple project assurances and required corrective actions at nearly a dozen academic institutions, and FDA has suspended clinical research at others.[8] OPRR/OHRP sanctions were imposed when numerous deficiencies and concerns regarding systemic protections for human subjects were

[5] OHRP maintains a list of "compliance determination" letters on its website at http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.htm; FDA lists clinical researchers who have been sanctioned at http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm; and the Office of Research Integrity lists debarred investigators at http://www.fda.gov/ora/compliance_ref/debar/default.htm.

[6] In June 1999, the Secretary of DHHS created a new office, the Office for Human Research Protection (OHRP), to replace the Office for Protection from Research Risks (OPRR), which had been responsible for oversight of research involving human participants at institutions receiving federal funds and implementing the 18-agency federal Common Rule. The location of OPRR had been debated for years. Three background papers prepared for NBAC pointed to difficulties in having the office responsible for ethical conduct housed under the director for extramural research at National Institutes of Health (NIH), effectively subordinate to the funding office for extramural research, and poorly positioned to exert influence over the NIH intramural research program (Fletcher, forthcoming; Gunsalus, forthcoming; McCarthy, forthcoming). The NBAC papers all cited a need to elevate the administrative hub for protecting human research participants up and out of NIH, but differed in whether the location should be within DHHS or in an independent executive agency. A committee convened by then NIH Director Harold Varmus recommended in June 1999 that OPRR be moved to the level of the DHHS Secretary and, among other things, that the Secretary create an external advisory committee for the office and that resources be increased for monitoring and enforcement (Office for Protection from Research Risks Review Panel, 1999). Less than six months after its creation, OHRP began a streamlined IRB registration and assurance process.

[7] Compliance determination letters indexed by month at http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.htm.

[8] Multiple project assurances are agreements between institutions and the federal government that pledge compliance with human subject regulations under 45 CFR 46. Suspension of these assurances effectively ceases research requiring IRB review. FDA actions include "clinical holds" on all or part of an institution's research under FDA human subject regulations (21 CFR 50, 21 CFR 56 and 21 CFR 312.120).

found. Deficiencies occurred in such areas as IRB membership, education of IRB members and investigators, institutional commitment, initial and continuing review of protocols by IRBs, review of protocols involving vulnerable persons, and procedures for obtaining voluntary, informed consent. Also in 1999 it was discovered that researchers with the U.S. Department of Veterans Affairs (VA) in West Los Angeles were performing risky research without obtaining participants' consent, leading to congressional hearings and a subsequent change in VA policies (see below) (U.S. House of Representatives, Committee on Veterans Affairs, 1999).

The Death of Jesse Gelsinger

Attention was already focused on the protection of human research participants when 18-year-old Jesse Gelsinger died in a phase I gene transfer study at the University of Pennsylvania in September 1999. He was a relatively healthy (i.e., medically stable) young adult with a genetic condition—ornithine transcarbamylase deficiency—who had suffered intermittent health crises because of his condition throughout his life but who was doing relatively well on medications when he entered the gene transfer trial (Gelsinger, 2000; Lehrman, 2000a,b). The details of the case are complex and to some extent contested. Although Gelsinger was aware that he was in a gene transfer study, FDA found that the consent form had been altered from that which had been approved and that data relevant to safety had not been reported. Questions were raised about whether some patients in the trial, including Gelsinger, fit the revised inclusion criteria and whether the IRB and relevant federal agencies were notified of adverse events that had occurred in studies with animals and in previous patients (Weiss and Nelson, 1999).

The Gelsinger case was heavily reported in the national media and drew the attention of clinical investigators and research administrators throughout the world. It also became the focus of a Senate hearing and commanded direct attention from the Secretary of DHHS, who subsequently requested the Institute of Medicine (IOM) study presented in this report (see discussion below) (Shalala, 2000; U.S. Senate, Subcommittee on Public Health, Committee on Health, Education, Labor, and Pensions, Subcommittee on Public Health 2000). Problems with the system of protections for those participating in research were already apparent in 1999, but the Gelsinger death brought a sharp escalation in attention because it resulted from the experimental intervention and failures in the system of protections more than his underlying condition.

A CALL FOR ACCOUNTABILITY

The events of the 1990s that led to this report continuously highlighted the need for reform of the system of protections for humans involved in research.

The rapid growth in the size of the research enterprise, the constant innovations in experimental tools and approaches, and growing demands on the review process from the public and research sponsors alike led PRIM&R and others to ask whether improvements could be gained by the establishment of standards for systems for the protection of humans, accompanied by a method for the measurement of compliance. Others argue that current ethical principles codified in the federal regulations and relevant international guidelines are sufficient. These observers argue that what is needed are more resources devoted to IRBs and regulatory agencies to ensure that protections are in place (Amdur, 2000; Snyderman and Holmes, 2000; Sugarman, 2000).

In 1999 and 2000, several groups moved forward with plans to develop standards for accreditation of IRBs and human research protection programs. These initiatives have come forward largely from two groups: one spawned from the PRIM&R effort and the other developed through a contract between NCQA and VA. The origins of both are discussed in Chapter 2.

STATEMENT OF TASK

In October 2000, the Secretary of DHHS asked the Institute of Medicine to conduct a two-phase study to address three interrelated topics involved in the protection of human research subjects. The three topics are (1) accreditation standards for HRPPPs[9], (2) the overall structure and functioning of activities for the protection of human research subjects, including but not restricted to IRBs, and (3) criteria for evaluation of the performance of activities for the protection of human research subjects.

The IOM response is being conducted in two phases. Phase 1, the subject of this report, focuses on accreditation standards for HRPPPs. The specific tasks for phase 1 are to

1. review and consider proposed HRPPP performance standards;
2. recommend standards for accreditation of HRPPPs, considering measures of structure, process, and performance, as well as resource sufficiency; and
3. recommend steps that the organizations and institutions conducting research and the federal government should take to collect and analyze data to monitor and evaluate how well the system for protecting human subjects is operating.

[9] In the course of committee deliberations, the term "human research participant protection program" was substituted for "human research review program" as the former term better reflected the system of oversight that the committee hopes will result from its recommendations.

Phase 2, will continue the 24-month study of the structure, function, and performance of activities for the protection of human research subjects.[10] The results of this future work will be presented as a separate report.

DEFINITIONS

In this section on definitions, the committee wishes to clarify its choice of terms to avoid confusion within this report and also to signal its awareness of the semantic difficulties, which are related to substantive and theoretical differences. Three questions regarding terminology are addressed below: (1) what should individuals who volunteer to be part of a research study be called? (2) what elements and research contexts should be included in an HRPPP? and (3) what is accreditation?

Subject or Participant?

The committee received disparate, sometimes directly contradictory advice about what to call those individuals who participate in research but who are not investigators. Those studied in human research have been called "subjects," "participants," "patients," "respondents," "partners," "interviewees," "probands," "volunteers," and other terms. More recently, additional consideration has been given to the status of individuals who are identified by virtue of their relationship to the person who is the subject of the research, either because of biological or familial ties or because of membership in the same social, ethnic, or racial group. However, some of the terms apply only in a particular research context.

Federal regulations and international guidelines refer to "human subjects" of research. The reason for this language is to distinguish the person being studied from the investigator, to make clear who is the object of study, and to signal a power asymmetry. The framework underlying the regulations is to "protect" the rights and interests of subjects, with the underlying premise being that those being studied are vulnerable when their interests conflict with those of science or investigators. The regulations are intended to make clear that when such conflicts arise, the human rights of subjects trump the scientific interests of investigators and their institutions.

As discussed earlier, the initial framework for HRPPPs grew out of reaction against studies that put humans at risk for the benefit of science, particularly against their will or without their informed consent. It was natural to classify them as "human subjects," to emphasize the power and information asymmetries, but without intending to imply a passive or demeaning role. This concept was further extended by focusing on "vulnerable" populations especially prone to coercion or at higher risk, such as children, prisoners, pregnant women, and

[10] For more information see http://www.iom.edu/hrrp.

those with diminished mental capacities. The "human subject" framework was fully intended to pit individual rights against collective interests, and therein lay its value.

This framework of protection conflicts, however, with an alternative framework that sees research as a good in itself. Advocates (including prospective "human subjects") have come to regard access to research as a right. AIDS activists argued for "drugs into bodies" and fundamentally reframed the debate about the role of individuals in research participation (Epstein, 1996). The same shift has spilled over into debates about women in health research, breast cancer research, and research on ethnic groups, minorities, and underserved populations (Batt, 1994; IOM, 1994, 1999; Love, 1995; Merkatz and Summers, 1997).

Involvement in research is a topic of special sensitivity to at least some members of minority populations; and what to call those who volunteer for research is a matter of serious debate, but no consensus has been reached. At the committee's public forum, one African-American speaker strongly urged the committee to abandon the term "human subject" because it was demeaning, locked into place a policy framework that emphasizes powerlessness and passivity, and cast the discussion in the penumbra of the Tuskegee Study (Ashe, 2001). Advocates concerned about American Indians, breast cancer, and mental illness have reiterated this recommendation to the committee. Yet, it was an African-American legal scholar who argued for use of the word "subject" because it rightly emphasizes real-world vulnerabilities and comports with established regulatory language.

Debates about words reflect not just differences in referents but also differences in rhetorical purposes. The term "subject" highlights the reality of information and power imbalances, whereas the term "participants" or "partners" reflects a moral aspiration. One expresses subjects' need to be protected, but the other expresses the regard for participants' direct contribution and involvement in an ideal research system.

Underlying practical differences exist beyond these political and moral differences. A human subject in one study may be a seriously ill patient deciding among experimental treatments under the guidance of a health care professional. Yet, the same regulations that cover the seriously ill patient cover a student of journalism interviewing prominent business figures, in which the "subject" may be considerably more powerful than the investigator, as well as those who respond to a survey (if it contains personal identifiers) and have only glancing contact with any investigator. Even within the confines of clinical trials for drugs, a person participating in the trial may truly be the healthy "subject" in whom a prospective drug is being tested for dose and toxicity, may be someone choosing among small twigs of an elaborate and extensive decision tree, or may be a desperately ill patient choosing among options that are all risky and experimental. Thus, no one word can fit snugly into all these situations.

NBAC devotes a section of its forthcoming oversight report to its choice of a term. In the end it has chosen to use the neutral word "participant" because it

avoids some sensitivities and is unlikely to be confused with investigators in context. This choice has a cost in that it diverges from formal regulatory language and loses the immediate sense of vulnerability that the regulatory language was intended to signal. Most members of the present IOM committee nonetheless concur with NBAC's choice, "participant," primarily because many of the committee's recommendations reinforce the aspiration to involve participants more directly in research and its oversight. The committee will therefore refer to "participants" except in contexts in which a more precise term is preferred.

What Is a Human Research Participant Protection Program?

The current framework for HRPPPs grew out of research conducted by a single investigator at a single institution that could assign protocol review to a single IRB. With the expansion of the scope and scale of research and particularly the expansion of privately funded research, a growing fraction of research falls outside this research institution framework. If the research design comes from a central sponsor—whether it is an agency gathering statistical data on the national population, an NIH institute, or a private firm testing a drug or a device—the participants in a trial may be drawn from dozens or even hundreds of places. In addition, the study may involve many research institutions and go outside traditional research sites into clinics and community hospitals or even (as in the case of surveys) into the general population. The power of each individual institution and its associated IRBs is limited to that institution. Under the current system, each IRB makes a separate and distinct determination that results in approval, disapproval, or modification of a research study. Collectively, the IRB rulings for the same protocol may result in disparate or even contradictory findings.

The committee's first task was to make recommendations about accreditation standards for "human research participant protection programs," a term by implication (tautologically) defined to be the unit of accreditation. As discussed in Chapter 3, the proposed NCQA and PRIM&R standards essentially assume the unit of accreditation to be

- VA facilities to be accredited by NCQA; or
- research institutions that conduct biomedical research and that have one or more IRBs.

This committee uses the term to embrace a set of functions and institutions somewhat wider than those contemplated in the draft standards to include boards that monitor the safety of clinical trials or that report serious and unexpected adverse events that arise from research and also to include research organizations not configured as academic research institutions (Figure 1-1). The key components of HRPPs are

- the organizational units responsible for designing, overseeing, and conducting research (which, for some research, includes research sponsors);
- the IRB reviewing that research;
- the investigators carrying out the research; and
- monitoring bodies (including data safety and monitoring boards; ombudsman programs; data collection centers; and reporting mechanisms for adverse events, complaints, and concerns); and
- the participants involved in the research

The term HRPPP and the various contexts in which it applies are further discussed below in an effort to clarify the scope of the committee's findings and recommendations.

The Centrality of Informed Consent

Informed consent is therefore also the heart of HRPPs. It is directly pertinent to accreditation standards and their use in the accreditation process because many of the most detailed aspects of federal regulations—and consequently, of both NCQA and PRIM&R standards—deal with the documentation of informed consent. This is an area in which the standards may be most onerous and in which a shift to the use of performance measures—ways of getting and documenting genuine informed consent that do not rely as heavily on formal written, signed documents, as current practice does—would be most welcome. The current formal, "contractual" practice is one of the most alien to investigators and study participants in many foreign countries (Marshall, forthcoming), and *documentation* is one of the most nettlesome issues that breeds conflict between investigators and IRBs despite nearly universal acceptance of the underlying ethical principle.

The empirical literature about the informed-consent process, cultural variations in how to interpret the ethical conduct of research, and diverse methods for obtaining and documenting informed consent will be reviewed in the committee's subsequent report. Even before that report appears, however, the committee notes that retrieval and documentation of informed consent are essential and are required by federal regulations, but accreditation bodies should strive to permit and even encourage experimentation with alternative methods to ensure informed consent within the parameters of current regulations. The waiver authority already present in the regulations for research involving minimal risk to participants (45 CFR 46.117(c) could be used to accumulate experience, with an eye to developing less intrusive but equally valid methods for obtaining informed consent for research involving more than minimal risk. Such methods could, in turn, produce measures of informed consent that are more effective and

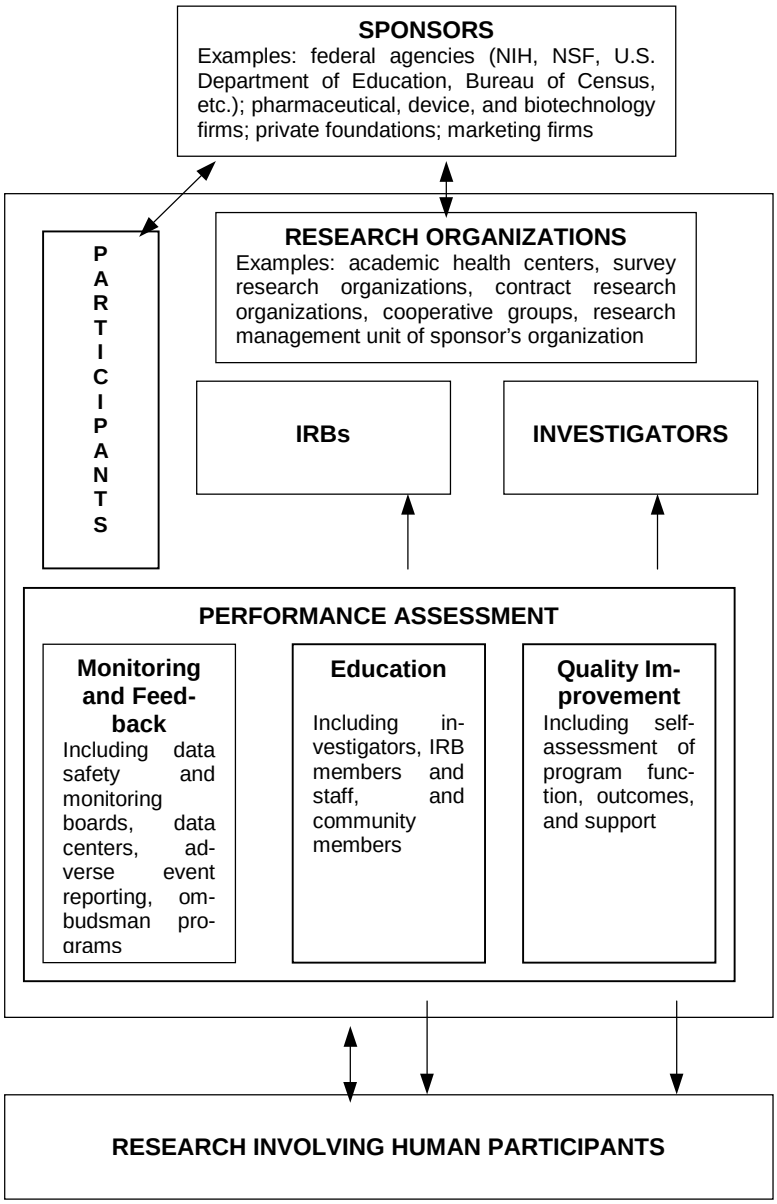

FIGURE 1-1 Human research participant protection programs. The components in the large box are all parts of an HRPPP. Arrows represent information flow pathways, not organizational responsibilities. All units within HRPPP should have formalized communication procedures.

less bureaucratic and that might eventually enable a shift in accreditation standards from documentation to assessment of genuine informed consent.

The Rise of Clinical Trials and Privately Funded Research

Clinical trials constitute only a subset of research, but they are an important subset. Clinical trials comprise a sizeable fraction of the studies that entail medical risks to participants and are a large and growing fraction of medical research. Also, on the basis of the growth of organizations dedicated to managing clinical trials and other evidence, it appears that the number of privately financed clinical trials has grown dramatically over the past decade (Rettig, 2000). Those trials conducted at a research institution with an HRPPP can be accommodated by attending explicitly to the roles and responsibilities of research sponsors. Many trials, however, are "multicenter trials" involving participants drawn from academic medical centers, private physicians' practices, community hospitals, clinics, and other institutions. Some of these may, in fact, lack an IRB.

In some cases, organizations that manage multicenter trials have developed, and these present a particular challenge to determination of the appropriate HRPPP unit. In cancer research, for example, several "oncology cooperative groups" have existed for decades to organize such trials, so that today 1,400 institutions participate. Community hospitals are also engaged in research through the Community Clinical Oncology Program, which includes 52 centers in 30 states (NCI, 1997). The National Cancer Institute is forming a central IRB and is revamping its support structure for clinical trials. This is driven in large part by the need to increase the scopes and scales of clinical trials (NCI, 2001).

For multicenter trials, research sponsors are often very large organizations for which clinical trials are only a small fraction of their work (e.g., pharmaceutical firms or NIH institutes), and so the sponsor may not be the appropriate unit for HRPP accreditation. When large organizations sponsor and conduct trials, however, they have organizational units that are responsible for trial oversight and that could apply for accreditation. In large multicenter trials, individual research institutions are at too low a level for meaningful accreditation because many such institutions are involved in the trial and none has meaningful control over the study design and overall safety. The appropriate locus of accreditation for multicenter clinical trials might prove to be different from that for research in general and might be focused on the organizations that have developed to manage the research, such as contract research organizations for privately funded trials or cooperative groups for both private and publicly funded trials. Accreditation bodies might devise a special set or subset of standards for such organizations.

Another option for multicenter trials is to focus on the IRB review step specifically. A research sponsor may pay for review by an IRB, constituted in compliance with FDA regulations for research involving human subjects but not affiliated with any particular research institution and not in control of the inves-

tigators, who are accountable instead to the research sponsor. Such organizations are discussed in further detail below.

Nonbiomedical Research

The committee heard about the potential problems of applying an oversight system designed to ensure the ethical conduct of clinical trials in medical research to other research methods. The United States requires review of federally funded research in disciplines outside medicine, but many other countries review only medical research. Although the principles of informed consent and the importance of oversight apply to all research, the principles will be applied in different ways when the risks are social rather than medical and when the goals of research may not be prevention, detection, or treatment of disease. Therefore, the risks and benefits of such projects will be analyzed differently from those of clinical trials, and such projects will require different kinds of expertise and sensitivities to different categories of research participants.

Research in anthropology, sociology, journalism, law, and economics, for example, require distinct methods. Furhter, distinct methods and issues apply to the gathering and analysis of data for national statistical databases. Student projects at a college or graduate school or even a high school education research initiative do not map neatly to IRB review mechanisms at an academic medical center. Interviews, surveys, oral histories, and other methods common to the social sciences must be reviewed in light of expertise in relevant fields.

In response to the committee's call for public comments, the committee did not hear pleas to exempt nonmedical research from oversight, but several groups expressed concern that the draft accreditation standards (in this case, the PRIM&R standards) would require elaboration of formal policies and documentation that would be irrelevant for IRBs primarily reviewing social science, behavioral research, anthropology, sociology, oral history, epidemiology, and population studies (Levine, 2001; Overbey, 2001; Shopes, 2001). The committee did hear suggestions to reduce paperwork, to develop criteria sensitive to social and behavioral research and to expand the categories of research exempt from review when the risks of nonmedical research are inherently low and informed consent can be "presumed" (e.g., by returning a survey form or answering questions in an interview) (Erickson, 2001; Rubin, 2001; Rudder, 2001).

Many of the policy options are relevant to the committee's subsequent report on the overall system of research oversight, but nonmedical research does raise some questions relevant to accreditation specifically. The American Association of University Professors has prepared a white paper on this topic (AAUP, forthcoming), and the Committee on National Statistics, collaborating with the Board on Behavioral, Cognitive, and Sensory Sciences (IOM), is commencing a study of research oversight for the social and behavioral sciences that should inform the present IOM committee's subsequent report. The committee

believes that in the meantime it will be important that emerging accreditation standards and the accreditation bodies that use them take this diversity of research into account and clearly indicate those mainly or solely applicable to clinical research (see further discussion in Chapter 2 and Recommendation 5).

Independent IRBs

The mandates and functions of independent IRBs are similar in scope to those of IRBs housed within an institution. Both types of review bodies and their administrative staffs function within a prescribed set of FDA regulations and according to guidance documents requiring initial review and protocol approval. Thereafter, ongoing review activities include monitoring of adverse events, oversight of recruitment activities, and review and approval of protocol amendments. The trend over the past decade has been for industry sponsors to conduct more multicenter studies outside of the institutional framework, thereby shifting the jurisdictional locus from the IRBs of individual institutions to independent (central) IRBs. Such boards review a growing fraction of research both in the United States and abroad. Thus, accreditation bodies need to develop standards or a subset of standards that embrace the independent IRB model.

Independent IRBs can stop a trial, but they do not employ investigators or have authority over them in the same way that the faculty at an academic health center does. The sections of the NCQA and PRIM&R draft standards on "research institutions" and "investigators" therefore do not apply directly to independent IRBs (Isidor, 2001). The operations of IRBs could, however, be accredited, and given their growing importance, independent IRBs should be included in any credible accreditation system. An independent IRB or group of IRBs administered by a single organization might be accredited, perhaps by using the subset of standards applicable to IRBs only, with oversight of investigators and the actual conduct of research performed through mechanisms other than accreditation (e.g., by FDA or OHRP review of sponsors and investigators). Accreditation of independent IRBs could be made contingent, for example, on ensuring that the sponsors from whom they accept work meet specific criteria. Sponsors should disclose whether a protocol has previously been disapproved by any IRB.

Most research reviewed by independent IRBs consists of clinical trials for drugs, devices, and biologics Guidelines for the ethical conduct of such clinical trials already exist, however. These are the . International Conference on Harmonisation Guideline for Good Clinical Practice (ICH-GCP) which apply to any research conducted under an investigational new drug application (IND) subject to FDA approval. If sponsors are operating under an IND or otherwise agree to abide by ICH-GCP guidelines, particularly if those guidelines were strengthened to ensure a stronger voice for research participants, independent IRBs could be accredited for their capacity to do a thorough review, leaving oversight of re-

search sponsors and investigators to FDA under existing regulations. Independent IRBs would be accredited only if they made their review contingent on the sponsors' agreement to ensure the ethical conduct of research under the sponsors' direct control, including the use of investigators who agree to abide by accepted standards.

Sponsors

To accredit HRPPPs as a system representing the complement of necessary activities that ensure the protection of human research participants, the responsibilities of research sponsors must also be included within the accreditation structure. Although existing FDA regulations, for example, assign the ultimate accountability for ensuring the management of ethical research to the sponsor, this does not alleviate the need for organizations seeking to run an HRPPP from incorporating this responsibility into their programs. In instances of clinical research involving drugs, devices, and other products under the purview of FDA regulations, FDA would continue to be the locus of enforcement. Another option would be to consider organizational units within sponsoring organizations as the unit for accreditation, but this would be an entirely new strategy and would entail the use of accreditation strategies drastically different from thosed used in the accreditation models that the committee considered.

The Role of the Research Participant

Those in the best position to judge the interests of individuals participating in research are the participants themselves or informed representatives of participant perspectives. This is both a moral principle and a practical fact. The central tenet of the Nuremberg Code and the first principle of *The Belmont Report* center on individual autonomy, honoring Immanuel Kant's categorical imperative to "Act so that you treat humanity, whether your own person or another, always as an end and never as a means only" (Kant, 1999, p. 566). Those participating in research are also in the best position to appreciate their wants and needs as a practical matter, and the principle of autonomy suggests that their wishes should be respected (Faden and Beauchamp, 1986). Although participants are often not in a position to judge the scientific value of a protocol, participant perspectives can improve the study design, review of protocols, and oversight of ongoing research. They may identify procedures that add only marginal technical value but that cause serious inconvenience or increase the risk to participants. Study designs that accommodate participant needs can improve recruitment and retention of participants and thereby strengthen the study. The presence of representatives of

study participants on study design and oversight panels also adds credibility to the review and monitoring processes among participants.[11]

Those developing accreditation standards would do well to directly involve focus groups, consent monitors, and participant representatives (e.g., those who themselves have been involved in past studies and who represent a genuine constituency) in specifying the desired outcomes to be incorporated into accreditation standards. In his book on accreditation, Michael Hamm cites the example of groups representing people with disabling conditions who were able to list desirable attributes of buildings that would permit access (Hamm, 1997). Participant involvement includes participation with the study design and representation on IRBs, monitoring bodies, and oversight and advisory bodies for research institutions.

Research Monitoring

Research monitoring was foremost among the problems identified by DHHS OIG (DHHS OIG, 1998a,b,c,d,e, 2000b,c,d). The main function of IRBs has been and will remain the review of protocols for proposed research to ensure that the research design is sound, that participants give their informed consent, and that selection of subjects is fair. IRBs are already busy with their current responsibilities, and research monitoring is an additional duty. IRBs therefore may not be the unit best able to carry out the monitoring of research. The committee believes that research monitoring—including adverse event reporting, data safety and monitoring boards, ombudsman programs, reporting mechanisms for concerns or complaints, and consent monitoring programs—should be defined as part of an HRPPP but not laid solely at the feet of the IRB component of an HRPPP.

Many elements of the ICH-GCP guidelines that relate to reporting of adverse events and other elements of research monitoring. Research under an FDA IND must comply with strict reporting requirements for adverse events, and the federal code requires reporting of "unanticipated problems posing risks to subjects".[12] Research monitoring is incorporated into NCQA standards but is not a central theme of the proposed PRIM&R standards, in which it is mentioned in only one documentation standard. The committee believes that adverse event reporting and research monitoring should be central elements of the system as a whole and, hence, also of any accreditation process intended to improve that system.

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[11] Involvement of the National Breast Cancer Coalition was instrumental, for example, in clinical trials of the drug herceptin, when early clinical trials were having difficulty recruiting participants. The National Breast Cancer Coalition became involved, however, only when it could directly participate in trial design and oversight (Bazell, 1998).

[12] 45 CFR 46.103 (b)(5)

Accreditation Versus Certification

The committee uses the term "accreditation" to refer to a process described in Chapters 2 and 3. That process is centered on an organization rather than individuals. The committee uses the term "certification" to refer to an individual. The National Association of IRB Managers, for example, has offered a certification examination since 1995, and the Applied Research Ethics National Association recently has launched a certification program for individuals who staff or chair IRBs (National Association of IRB Managers, 2001; PRIM&R, 2001a).

Certification is offered only to those with demonstrated experience and entails passing a test of knowledge about protection of human research participants. Certification has been discussed for investigators who conduct research involving human participants. For example, the government of the United Kingdom licenses those doing animal research and research on in vitro fertilization and embryo research. In the United States, however, no structure to carry out national certification of U.S. investigators exists. NIH and several universities (e.g., Case Western Reserve University and the University of Rochester), for example, have recently adopted requirements that investigators take a World Wide Web-based interactive test that demonstrates knowledge of human research protections before they can seek IRB approval of a protocol (Case Western Reserve University, 2001; Chadwick and Liders, 2000; Office of Human Subjects Research, National Institutes of Health, 2001). A national certification requirement for investigators, however, would be a major step entailing the development of a substantial infrastructure. For this reason, the committee does not consider the issue of certification in this report.